Review: Smooth-muscle relaxants treat abdominal pain and loperamide reduces diarrhea in the irritable bowel syndrome

Jailwala J, Imperiale TF, Kroenke K. **Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials.** Ann Intern Med. 2000 Jul 18;133:136-47.

QUESTION

What is the effectiveness of pharmacologic agents for the treatment of the irritable bowel syndrome (IBS)?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 1999), EMBASE/Excerpta Medica (1980 to 1999), PsycINFO (1967 to 1999), and the Cochrane Controlled Trials Registry with terms that included colonic diseases, functional, irritable, spastic, bowel, and colon and by manually searching bibliographies of relevant studies.

STUDY SELECTION

Published studies in the English language were selected if they examined use of a pharmacologic treatment for IBS on > 10 adult patients for ≥ 2 weeks; included a placebo group; reported an outcome measure of global status or individual symptoms, or both, of IBS; and used a randomized, double-blind, parallel-group or crossover design.

DATA EXTRACTION

Data were extracted on the diagnostic criteria for IBS, participant characteristics, interventions, study design, methodologic quality (scored between 1 and 5 with a higher score representing higher quality; studies with a score ≥ 4 were classified as "high quality"), and outcomes. Pharmacologic agents were classified as having "positive" effectiveness if the study reported significant improvement in global status or individual IBS symptoms; otherwise, they were classified as having "negative" effectiveness.

MAIN RESULTS

70 studies (4836 patients, median age 38 y, 68% women, mean study duration 7.5 wk, mean methodologic quality score 3.2) met the inclusion criteria. 66 studies evaluated a single agent, and 4 evaluated a combination of ≥ 2 agents. The most common pharmacologic classes of agents were smooth-muscle relaxants, bulking agents, prokinetic agents, psychotropic agents, and loperamide. Of 16 studies of smooth-muscle relaxants, 13 showed positive effectiveness; 7 had high quality, and all of them showed an improvement in abdominal pain. Of 13 studies of bulking agents, 4 showed positive effectiveness; 7 had high quality, and of these, 3 showed positive effectiveness. Of 6 studies of prokinetic agents, 2 showed positive effectiveness; 4 had high quality, and of these, 1 showed positive effectiveness. All 7 studies of psychotropic agents showed positive effectiveness, and 1 had high quality. All 4 studies of loperamide showed an improvement in diarrhea, and 2 had high quality.

CONCLUSIONS

Most studies on pharmacologic treatment of the irritable bowel syndrome examined smooth-muscle relaxants and bulking agents. Smooth-muscle relaxants are effective for relieving abdominal pain, and loperamide is effective for reducing diarrhea. However, data are inconclusive for the effectiveness of other pharmacologic agents for the irritable bowel syndrome.

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COMMENTARY

IBS is still a diagnosis of exclusion despite the fact that criteria for making a positive diagnosis have been established and widely disseminated. Organic lesions that resemble symptoms commonly seen in IBS must be excluded before initiating treatment (1). The traditional treatment for IBS has been a combination of symptomatic therapy, reassurance, education, and lifestyle modification. Patients with milder disease can usually be managed conservatively, even for the short term. Other patients can be prescribed a combination of psychotherapy, psychopharmacotherapy, and pharmacotherapy, which generally has variable success.

The review by Jailwala and colleagues evaluates the available therapeutic trials. Considering the varied presentation of IBS, lack of uniform diagnostic criteria, and initial difficulties in defining the condition, a substantial number of trials did not meet rigorous scientific standards. The authors stated that smooth-muscle relaxants for abdominal pain and loperamide for diarrhea were the only agents with clinical effectiveness. Although results for other therapeutic agents were inconclusive, the authors expressed an optimistic view that, as the pathophysiology of IBS becomes better understood, it is likely that subgroups of patients with specific sets of symptoms may be responsive to targeted therapies.

Many new therapies that focus on modulating neurotransmitters in the "brain–gut" axis are currently being studied. Recent interest in serotonin receptors and serotonin-mediated motor activity in the gut has led to the development of new treatment options for the management of the more distressing symptoms associated with IBS. The type-3 serotonin receptor ($5\text{-}HT_3$) stimulates extrinsic enteric sensory nerves, thereby lowering visceral pain thresholds, a generally accepted component of IBS (2).

The study by Camilleri and colleagues involved an impressive number of women who had abdominal pain and principally diarrhea-predominant IBS. The authors were able to show reasonable, although not overwhelmingly impressive, therapeutic efficacy of the $5\text{-}HT_3$ antagonist alosetron for control of mild-to-moderate symptoms.

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Alosetron was effective and safe for relieving abdominal symptoms in women with the irritable bowel syndrome

Camilleri M, Northcutt AR, Kong S, et al. **Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial.** Lancet. 2000 Mar 25;355:1035-40.

QUESTION

What is the effectiveness and safety of alosetron in women with the irritable bowel syndrome (IBS)?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, outcome assessors, and statisticians),* placebo-controlled trial for 12 weeks with 1-month follow-up.

SETTING

119 centers in the United States.

PATIENTS

647 women ≥ 18 years of age (mean age 46 y, 93% white) who had IBS for ≥ 6 months, had normal colonic anatomy, were diarrhea predominant or had alternating bowel patterns (diarrhea and constipation), had a mean daily abdominal pain and discomfort score between 1.0 and 3.3 on a 5-point scale (0 = none to 4 = severe), and a mean daily stool consistency score ≥ 2.5 on a 5-point scale (1 = very hard to 5 = watery). Exclusion criteria were constipation-predominant IBS; pregnancy, breast-feeding, or potential for childbearing; unstable medical or other gastrointestinal disorder; major psychiatric disorder; substance abuse in the previous 2 years; abnormal aspartate aminotransferase, alanine aminotransferase, or serum creatinine levels; hyperthyroidism or hypothyroidism; non-skin malignancy in the previous 5 years; investigational drug use 30 days before study; or use of specified drugs. Follow-up was 80%.

INTERVENTION

Women were allocated to twice-daily oral alosetron, 1 mg (n = 324), or placebo (n = 323) for 12 weeks. Study drugs were taken before meals.

MAIN OUTCOME MEASURES

Adequate relief of abdominal pain and discomfort; improvements in urgency, stool frequency, and stool consistency; and adverse events.

MAIN RESULTS

Analysis was by intention to treat. Alosetron had a higher rate of achieving adequate relief of abdominal pain and discomfort {P = 0.001}† (Table) and decreased urgency, stool frequency, and stool consistency (i.e., increased stool firmness) (P < 0.001) than did placebo. Alosetron was associated with a higher risk for constipation than was placebo {P < 0.001}† (Table), but groups did not differ in the rate of reporting ≥ 1 adverse events {P = 0.07}†.

CONCLUSION

Alosetron was effective and well tolerated in relieving abdominal pain and discomfort in women with the irritable bowel syndrome.

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*See Glossary.

†P values calculated from data in article.

Alosetron vs placebo in women who have had the irritable bowel syndrome > 3 months‡

Outcomes at 1-month follow-up	Alosetron	Placebo	RBI (95% CI)	NNT (CI)
Relief of abdominal symptoms	41%	29%	41% (14 to 75)	8 (5 to 22)
			RRI (95% CI)	NNT (CI)
Constipation	30%	3%	854% (415 to 1685)	4 (3 to 5)

‡Abbreviations defined in Glossary; RBI, RRI, NNT, and CI calculated from data in article.

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Alosetron (Lotronex) is the first serotonin-subtype antagonist to be examined in a large clinical trial. Unfortunately, alosetron's adverse effects have led to its recent voluntary withdrawal by its manufacturer, Glaxo Wellcome. This decision followed discussions with the U.S. Food and Drug Admini-stration, prompted by postmarketing reports of serious adverse effects, including severe constipation, ischemic colitis, and death (unproved association).

IBS is a chronic disorder with frequent relapses and substantial morbidity, although no mortality is caused by the disease itself. Therefore, the decision to initiate long-term pharmacotherapy should not be taken lightly. Only further trials and postmarketing surveillance strategies will determine whether the class of drugs represented by the ill-fated alosetron will be safe and better than smooth-muscle relaxants and loperamide and their combination with other interventions.

As investigators more accurately classify various subgroups of IBS, understand their unique pathophysiologies, and study the effects of the emerging therapeutic agents, targeted therapeutic interventions will become better defined. A supportive physician–patient relationship is necessary regardless of the therapeutic regimen. The availability of therapies that selectively antagonize the factors responsible for IBS symptoms adds a scientific dimension to the management of a very common, poorly understood, and challenging disorder.

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